A retrospective study of one versus two cm excision margins for cutaneous malignant melanomas thicker than two mm

Type of study Original Article

Robert E. Hunger, M.D., Ph.D. [1], Sarina Angermeier[2], S. Morteza Seyed Jafari, M.D.[2,3], Adrian Ochsenbein, M.D.[4], Maziar Shafighi, M.D.[2*]

1 University clinic for Dermatology, Bern University Hospital, Inselspital, Bern, Switzerland

2 University clinic for Plastic, Reconstructive and Hand Surgery, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland

3 Graduate School for Cellular and Biomedical Sciences, University of Bern, Switzerland.

4 University clinic for Medical Oncology, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland

***Corresponding author**

Maziar Shafighi

University clinic for Plastic, Reconstructive and Hand Surgery, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland

Tel: +41 31 632 8014

E-Mail: maziar.shafighi@insel.ch

Running head one versus two cm excision margins for melanomas thicker than 2 mm

ABSTRACT

Background**:** Most guidelines recommend at least two cm excision margin for melanomas thicker than two mm.

Objective: We evaluated whether one or two cm excision margins for melanoma (> 2 mm) result in different outcomes.

Methods: This is a retrospective cohort study on patients with melanomas (> 2 mm) who underwent tumor excision with one cm (228 patients) or two cm (97 patients) margins to investigate presence of local recurrences, locoregional and distant metastases, disease-free and overall survival.

Results: Three hundred twenty-five patients with mean age of 61.84 years and Breslow thickness of 4.36 mm, were considered for the study with a median follow-up of 1852 days (1995- 2012). There was no significant difference in the frequency of locoregional and distant metastasis between the two groups (P = 0.311, 0.571). The survival analysis showed no differences for disease-free (P = 0.800; HR, 0.948; 95% CI 0.627 to 1.433) and overall-survival (P = 0.951; HR, 1.018; 95% CI 0.575 to 1.803).

Limitations: The study was not prospectively randomized.

Conclusions: Our study did not show any significant differences in important outcome parameters like local- or distant metastases, overall survival. A prospective study testing one versus two cm excision margin is warranted.

Key words Disease free survival; Margin of excision; Melanomas thicker than 2 mm; Metastases; Overall survival; Recurrences

INTRODUCTION

One of the major controversies in the primary management of melanoma is how much surrounding normal skin should be excised around a primary cutaneous melanoma.[1-4] Balancing cosmesis, function and morbidity with oncologic outcomes requires careful decision-making with respect to determination of the appropriate margins.[5] Inadequate excision margins increase the risk of local recurrence.[6] Conversely, unnecessarily large margins of excision generate greater morbidity and increased costs.[4] Overall survival, disease-free survival, and local recurrence rates are not improved by excision margins greater two cm.[7] Therefore, a two cm excision margin is recommended for melanomas thicker than two mm in most clinical guidelines.[4,7]

In our clinics a 1cm excision margin is the approved standard by the regional Melanoma Board for melanoma thicker than two mm, whereas external consultants operated with a two cm excision margin. We now analyzed in a retrospective study over a period of 16-years whether 1 cm surgical excision margin has caused any disadvantages in important outcome parameters, in comparison to two cm margins.

METHODS

Study Population

We performed a population-based survey of melanoma management (registered in ClinicalTrials.gov, trial number NCT02088762) using a database of patients from the Bern University Hospital. The study period ranged from May 1995 to May 2012, with follow-up until the end of July 2013. All cases of single, primary, localized, cutaneous melanoma tumors with > two mm thickness without evidence of metastasis at the time of surgery and treated by excision of the lesion were included in the study. Patients without documented surgical margins or follow-up were excluded. This study was conducted in accordance with the standards of the Ethical Committee of the Canton of Bern (KEK number: 24-08-10) on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Procedures

We collected data on patient gender, age, tumor location, tumor type, Breslow thickness, and presence of ulceration, distant and locoregional metastases. All surgeons were board certified and accredited members of an established cancer cooperative group.

During the 17-year time period, two consultants performed primary melanoma excision according to the current accepted guidelines, using a 2 cm margin (two cm group). All other consultants excised all melanoma in accordance with our regional Melanoma Board approved guideline with a one cm margin irrespective of Breslow thickness (one cm group). Thus, the excision margins were dependent on the referral to the individual consultant. In all cases, sentinel lymph node biopsies were taken. An experienced pathologist from the University Hospital Bern reviewed the excised tissues and the slides were also evaluated by a panel of melanoma pathologists, who independently reviewed a representative histologic section of each.

In the current study, local recurrences can represent either persistent disease due to inadequate initial excision or true recurrence adjacent to the scar after adequate prior wide local excision and usually have an in situ component, or they may represent satellite metastases. Locoregional recurrence of melanoma after initial resection was defined as recurrence at the site of the primary lesion, regionally in the draining lymph node basin, or anywhere in between (local recurrence cases were not included).[8-10] Spreading from the original (primary) tumor to distant organs or distant lymph nodes was considered as distant metastases.[11]

Local recurrence rates, locoregional and distant metastases, death attributed to melanoma, disease-free survival, and overall survival were compared between the two groups.

Statistical Analysis

All analyses were conducted using the Statistics Package for the Social Sciences (spss; SPSS Inc., Chicago, IL, USA) version 21.0. All p values relate to two-sided tests with an alpha level of 0.05. For categorical patient characteristics, Fisher's exact test was used to detect differences between groups. Disease-free survival was estimated using the Kaplan-Meier method. The confidence intervals of hazard ratios for Cox regression and overall survival (for time-to-event variables) were calculated. P value was based on the Log Rank (Mantel-Cox) test to check whether the two groups had different overall survival functions. P value < 0.05 was considered significant.

RESULTS

Of all patients with malignant melanoma treated in our center between May 1995 and May 2012, 325 (138 female, 187 male) patients with melanoma thicker than 2 mm with a median age of 61.84± 14.71 years (mean ± SD) fulfilled the inclusion criteria (Fig 1). The median follow-up for the patients was 1852 days. The mean ± SD Breslow's depth of the study patients' primary melanoma tumors was 4.36 ± 3.99 mm (2.10 – 45.00 mm). Two hundred twenty lesions (67.7 %) revealed an infiltration thickness≤ four mm, while 105 (32.3 %) were thicker than four mm. Nodular melanoma was the most frequent (68.3 %) and amelanotic melanoma the least frequent (1.8 %) type in our study population. Furthermore, the trunk area was the most frequent primary tumor location (39.4%). One hundred forty patients (43.1 %) had ulceration in their tumors, 106 patients (32.6 %) presented with positive sentinel lymph node biopsies, and death was attributable to melanoma in 54 patients (16.6%).

Two hundred twenty eight patients underwent tumor excision with a one cm skin margin while the tumors of the other 97 patients were excised with a two cm margin.

Statistical analysis of tumor characteristics (tumor thickness, primary tumor location, tumor type, and sentinel lymph node metastasis) did not reveal significant differences between the two groups, except for ulceration, which was detected significantly more often in the one cm group (Table 1).

Local recurrence occurred in 11 patients (3.4 %), locoregional metastases in 74 patients (22.8 %) and distant metastases in 77 (23.7 %). Although ulceration was seen more frequently in the one cm group, this did not result in a significant difference in local recurrence ($P = 0.739$), locoregional ($P = 0.311$) and distant metastases ($P = 0.571$) during the follow-up period. Death attributable to melanoma was also not significantly different between our study groups (18.8 % vs. 18.6 %, respectively) (Table 2).

Kaplan-Meier methods comparing disease-free and overall survival did not reveal a significant difference between the one cm group and the two cm group (P = 0.800 and 0.951, respectively). In Cox regression analysis of the patients with one cm excision margins vs. the patients with two cm excision margins, the estimated hazard ratios for disease-free survival and overall survival were 0.948 (95% confidence interval, 0.627 to 1.433) and 1.018 (95% confidence interval, 0.575 to 1.803), respectively (Tables 3, Fig 2-3).

DISCUSSION

Guidelines for melanoma treatment emphasize the importance of complete surgical excision.[12-15] However, selection of an adequate excision margin is one of the major controversies in the management of primary cutaneous melanomas, especially in melanoma thicker than two mm.[1, 3, 4] In light of the tendency to narrow the excision margins in primary melanoma thicker than two mm treatment, Gillgren, P et al. performed a randomized controlled trial in this patient group that compared a two cm versus a four cm surgical resection margin. Their findings suggested that a two cm resection margin is sufficient and safe for patients with cutaneous melanoma thicker than two mm.[3] As a result, currently, most protocols suggest at least a two cm excision margin for melanoma > two mm in depth.[16-18]

In order to follow this way to have a narrower but safe excision margins in primary melanoma treatment, we retrospectively analyzed the outcome of patients with melanomas thicker than two mm (2.10 – 45.00 mm in thickness) using a one or a two cm excision margin. Although our study was not prospectively randomized, the two study population were balanced for important prognostic factors with the exception of ulceration, which was more frequent in the group with narrower excision margin (Table 1). In this study, we did not detect a statistically significant increase in locoregional metastases, distant metastases or a decrease in disease-free or overall survival in patients undergoing a resection with only 1 cm margin.

We observed more locoregional and distant metastases in the patients with two cm excision margins, but these differences were not statistically significant. Similarly, Gillgren et al. reported less distant metastasis in the group with narrower excision margins (two cm) versus the wider excision (four cm). This difference might raise the idea that selection of wider excision margins may increase the risk of locoregional and distant metastases.

Gillgren et al. reported that 14.53% of patients died by melanoma,[3] while death attributable to melanoma was seen in 16.6 % of our patients, which was not significantly different between the groups in our study ($P = 0.625$). Thomas et al. reported deaths in 28.26% of the group with 1 cm margins and 23.49 % of the group with 3 cm margins.[4] Moreover, Thomas et al. found a significant increase in the risk of death from melanoma associated with a narrow margin of excision in comparison to a wide margin after evaluation of their results and Swedish Melanoma Study Group trial ($P = 0.008$).[4, 19]

Furthermore, Kaplan-Meier methods and Cox regression analysis of our groups showed no evidence of significant differences in disease-free survival and overall survival. Likewise, in Thomas et al.'s study on high-risk melanoma, a similar overall survival rate ($P = 0.6$; HR, 1.07; 95% confidence interval 0.85 to 1.36) was reported between the groups with 1 cm and 3 cm excision margins. Nevertheless, due to the increased risk of melanoma related death in the group with narrow excision margins, the authors concluded that the use of a one cm margin should be avoided in patients with melanomas $\geq$ 2 mm thickness.[4]

In summary, despite various studies, clear evidence that increasing excision margins improves overall-survival is currently missing.[16] Furthermore, decision about the need for two cm margins for thicker melanomas is still an important controversy. As a result there is a demand for further studies to overcome these issues. We believe that modification of current approved guidelines which are based on important clinical studies should be only performed carefully after implementation of prospective randomised multicenteric clinical trials. However, despite several limitations (being retrospective, and non-randomized, and having relative short follow-up), the result of the current study suggests that excision of melanomas thicker than two mm with one cm excision margin is safe and results in a similar outcome as a two cm excision margin. Therefore, this study highlights the possible hope for future, and may provoke the important melanoma centers to set up new randomized controlled trials with longer follow-up to revise current melanoma guidelines.

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Figure:

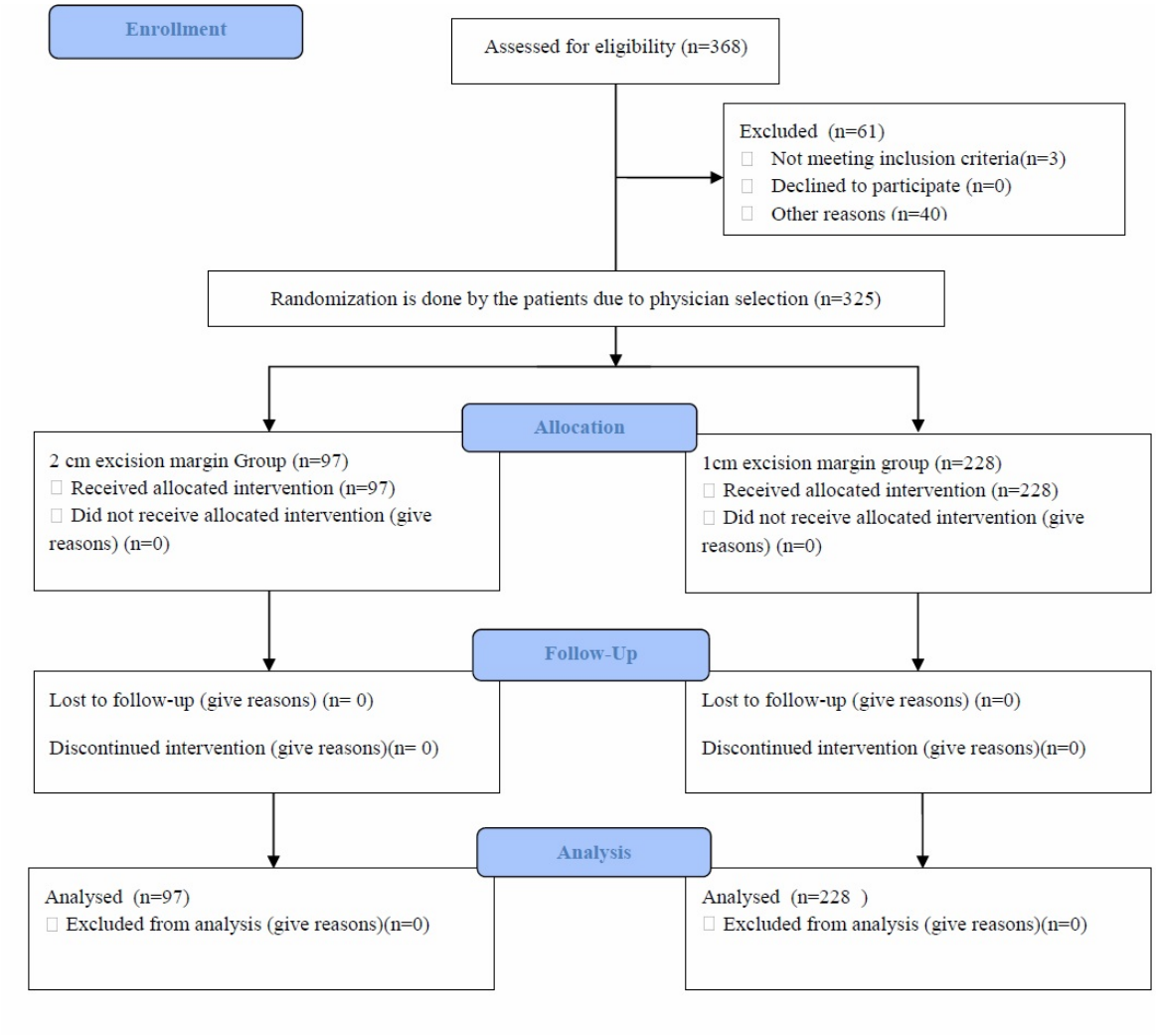
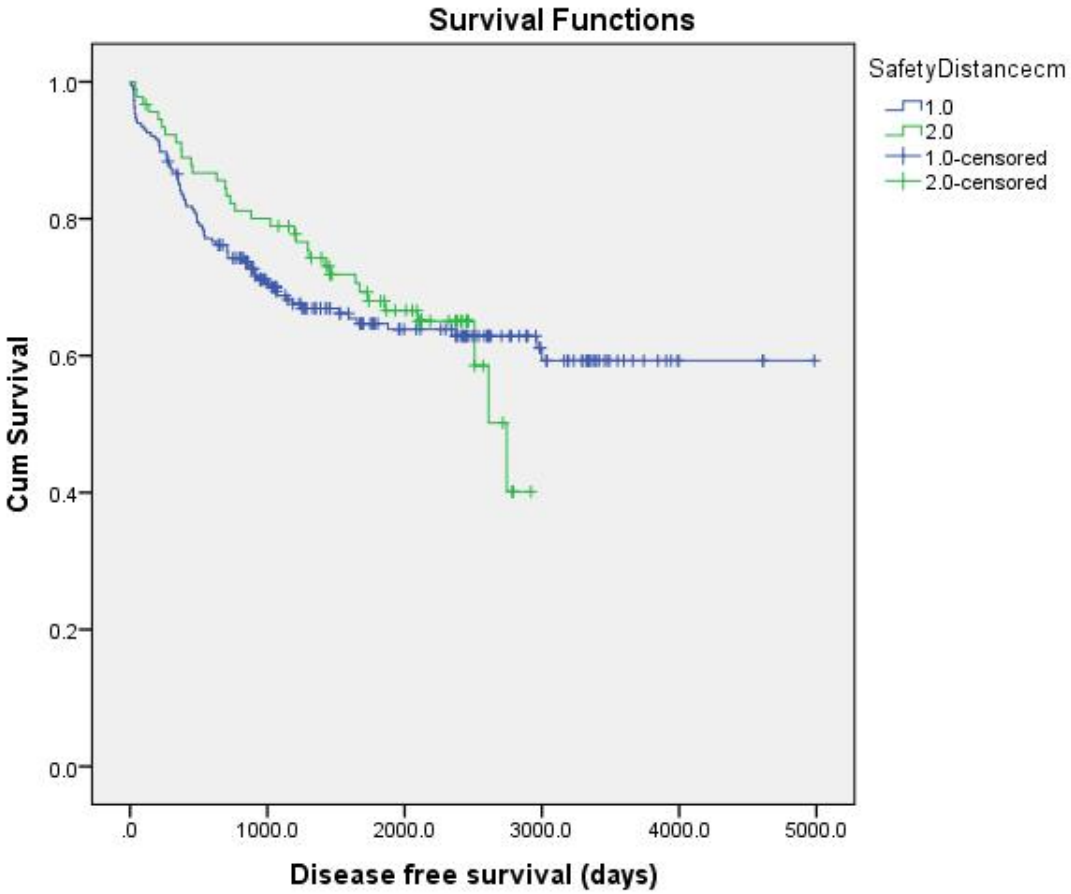


Fig. 1. Patient disposition



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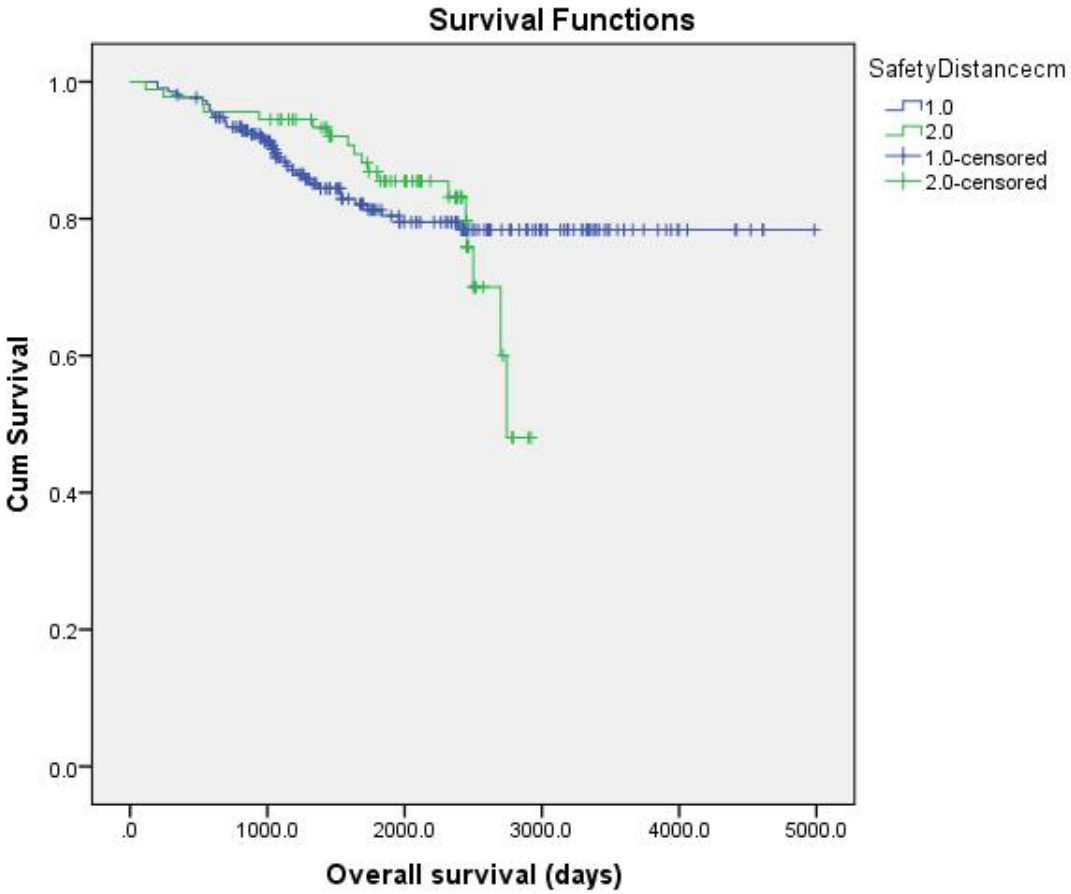
258 Fig. 2. Disease-free survival according to primary melanoma site (log-rank test, $P = 0.800$).



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260 Fig. 3. Overall survival (log-rank test, $P = 0.951$)

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Tables:

TABLE 1. Study patients' characteristics

Characteristics		Margin of surgery		*P*
		1 cm	2 cm	
Mean follow-up in years		5.18	5.51	0.207
Tumour thickness [Breslow] (Mean ± SD mm)		4.22 ± 2.81	4.67 ± 5.90	0.479
Sex	**No. of Female patients (percent)**	98 (42.98%)	40 (41.24%)	0.807
	No. of Male Patients (percent)	130 (57.02%)	57 (58.76%)	
Primary tumour location **No. (percent)**	**Head and neck**	47 (20.61%)	11 (11.34%)	0.119
	Trunk	82 (35.96%)	46 (47.42%)	
	Upper extremity	44 (19.30%)	16 (16.49%)	
	Lower extremity	55 (24.12%)	24 (24.74%)	
Tumour type **No. (percent)**	**Nodular melanoma**	148 (64.91%)	74 (76.29%)	0.190
	Superficial spreading melanoma	52 (22.81%)	16 (16.49%)	
	Acral lentiginous melanoma	9 (3.95%)	5 (5.15%)	
	Lentigo maligna melanoma	7 (3.07%)	0 (0.00%)	
	Desmoplastic melanoma	7 (3.07%)	1 (1.03%)	
	Amelanotic melanoma	5 (2.19%)	1 (1.03%)	
Positive sentinel lymph node biopsy	**No. of positive result (percent)**	68 (29.82%)	38 (39.17%)	0.121
Ulceration	**No. of positive result (percent)**	108 (47.37%)	32 (32.98%)	0.020

TABLE 2. Study patients' follow-up characteristics

Characteristics	Margin of surgery		Exact Sig. (2-sided)
	1 cm	2 cm	
Local recurrence, (percent)	7(3.07%)	4(4.12%)	0.739
Locoregional metastases, (percent)	48(21.05%)	26(26.80%)	0.311
Distant metastases, (percent)	52 (22.81%)	25 (25.77%)	0.571
Death attributed to melanoma, (percent)	36 (15.79%)	18 (18.56%)	0.625

TABLE 3. Means for disease free survival and overall survival Time

Margin	Mean[a] for DFS Time				Means for OS Time			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
1cm	3289.17	157.72	2980.03	3598.31	4150.41	125.75	3903.94	4396.89
2cm	2139.09	110.38	1922.76	2355.43	2551.48	76.19	2402.134	2700.82
Overall	3253.04	135.34	2987.78	3518.30	4085.29	111.62	3866.50	4304.07